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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/955,485	09/19/2001	Michael A. Moskowitz	031695.0031	7759

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EXAMINER
SPIVACK, PHYLLIS G

ART UNIT	PAPER NUMBER
1614	15

DATE MAILED: 08/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary

Application No.	Applicant(s)
09/955,485	Moskowitz et al.
Examiner	**Art Unit**
Phyllis G. Spivack	1614

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *May 23, 2003* .

2a) ☐ This action is **FINAL.** 2b) ☒ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *20-35* is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *20-35* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s). *13, 15*
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

An Amendment and Response filed May 23, 2003, Paper No. 12, is acknowledged. Claims 20-35 remain under consideration.

An Information Disclosure Statement filed May 23, 2003, Paper No. 13, is acknowledged. A second Information Disclosure Statement was received by the Examiner on August 7, 2003, Paper No. 15. All references have been reviewed.

Following an amendment to claim 35 wherein the claim is now independent, the objection of record is withdrawn.

In the last Office Action claims 20, 21, 23, 24 and 28 were rejected under 35 U.S.C. 103 as being unpatentable over Myslivecek et al., Neuroscience (abstract). It was asserted Myslivecek teaches the substantially contemporaneous administration of the NO-increasing agent, L-arginine, with the physiologically active composition comprising dopamine, in the brain.

Applicants argue Myslivecek fails to disclose a method of increasing cerebral bioavailability of a physiologically active composition and that any of a variety of mechanisms might have been indicated.

Applicants' arguments have been given careful consideration but are not found persuasive. The rejection of record is repeated for claims 20 and 28 for the reasons of record. The rejection of claims 21, 23 and 24 is withdrawn because these claims are directed to administration into the blood stream.

L-arginine, an NO-increasing agent, and dopamine, a physiologically active composition, are administered into the lateral cerebral ventricles. Myslivecek teaches there was an increased

dopamine level as a result of the substantially contemporaneous administration of the two agents which resulted in a positive therapeutic effect.

Claims 29-35 were rejected in the last Office Action under 35 U.S.C. 103 as being unpatentable over Werner et al., Proceedings of the Society for Experimental Biology and Medicine (abstract). It was asserted Werner teaches the requirement of various cofactors as NADPH and tetrahydrobiopterin for the conversion of L-arginine to nitric oxide to take place.

Applicant's arguments with respect to the rejection of record of claims 29-35 under 35 U.S.C. 103 have been considered but are moot in view of the new ground of rejection.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29-35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Cooke et al., U.S. Patent 5,945,452.

Cooke teaches a formulation consisting of a mixture of L-arginine and L-lysine to enhance the level of endothelial nitric oxide in the vascular system. See columns 19 and 20, claims 1 and 8, where NADPH or tetrahydrobiopterin is administered along with L-arginine and L-lysine. L-lysine may be considered a physiologically active component and L-arginine is an NO-increasing agent. NADPH and tetrahydrobiopterin are the agents that increase the production of NO by

preexisting ecNOS, as required by claim 31. The claims differ in that the pharmaceutical compositions disclosed in the reference are used to inhibit the development of atherosclerosis, restenosis or thrombosis. However, intended use of composition claims confers no patentable weight to the claims. In re Hack, 114 USPQ 161. One skilled in the art would have been motivated to prepare a pharmaceutical composition comprising L-arginine and L-lysine and either NADPH or tetrahydrobiopterin to treat various vascular diseases in view of the teachings of Cooke.

Claims 20-28 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for increasing the cerebral bioavailability of simvastatin, does not reasonably provide enablement for increased bioavailability of any physiologically active composition. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The claims are directed to increasing cerebral bioavailability of a physiologically active composition comprising administering an NO-increasing agent. The specification provides support for a method involving only simvastatin.

Attention is directed to In re Wands, 8 USPQ2d 1400 where the court set forth factors to consider when assessing whether or not a disclosure would require undue experimentation. These factors are:

1) the quantity of experimentation necessary

2) the amount of direction or guidance provided

3) the presence or absence of working examples

4) the nature of the invention

5) the state of the art

6) the relative skill of those in the art

7) the predictability of the art and

8) the breadth of the claims.

The instant specification fails to provide guidance that would allow the skilled artisan background sufficient to practice the instant invention without resorting to undue experimentation in view of further discussion below.

The nature of the invention, state of the prior art, relative skill of those in the art and the predictability of the art

The claimed invention relates to increasing cerebral bioavailability of any physiological agent comprising administering an NO-increasing agent such as L-arginine.

The relative skill of those in the art is generally that of a Ph.D or M.D.

Each particular physiologically active agent has its own specific characteristics. The unpredictability observed with single agent therapy is compounded when a combination of agents is employed. The broad recitation "a physiologically active composition" is inclusive of many compounds that are structurally unrelated.

It is clear the art to which the present invention relates is highly unpredictable and unreliable with respect to conclusions drawn from laboratory data extrapolated to clinical efficacy.

The breadth of the claims

The claims are very broad and inclusive of a plethora of physiologically active compositions.

The amount of direction or guidance provided and the presence or absence of working examples

The working example is limited to the combination of simvastatin and L-arginine.

The quantity of experimentation necessary

Applicants have failed to provide guidance as to which particular physiologically active compositions, other than simvastatin, in combination with which other NO-increasing agents, other than L-arginine, would be preferred for increasing cerebral bioavailability. The skilled artisan would expect the interaction of a particular combination of drugs to be very specific and highly unpredictable absent a clear understanding of the structural and biochemical basis for each agent. The instant specification sets forth no such understanding nor any criteria for extrapolating beyond the combination of simvastatin and L-arginine. Even for the combinations set forth, no direction is provided for administration other than parenteral. Absent a reasonable *a priori* expectation of success for using a particular chemotherapeutic combination to increase cerebral bioavailability, one skilled in the neurology art would have to test extensively many combinations of agents to discover which particular compositions and agents show the desired result to that particular combination. Since each prospective embodiment, as well as future embodiments as the art progresses, would have to be empirically tested, undue experimentation would be required to

practice the invention as it is claimed in its current scope. The specification provides inadequate guidance to do otherwise.

No claim is allowed.

Any inquiry concerning this communication should be directed to Phyllis Spivack at telephone number 703-308-4703.

August 17, 2003

Phyllis Spivack

PHYLLIS SPIVACK
PRIMARY EXAMINER